Brief Report

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Characteristics of subcutaneous tissues at the site of insertion of peripheral infusion in patients undergoing paclitaxel and carboplatin chemotherapy

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Summary **Paclitaxel, a taxane, is frequently administered intravenously as an anticancer agent. When a peripheral intravenous catheter is used for paclitaxel infusion, clinical nurses often observe signs such as slight swelling at the catheter placement site, lack of blood return, and difficulty in continuing the infusion. However, the cause(s) of such phenomena at the puncture site has not yet been elucidated. The aim of this study was to obtain ultrasonography images of subcutaneous tissues and veins of patients undergoing paclitaxel and carboplatin chemotherapy and compare ultrasonography images taken immediately before catheter removal with those of patients receiving other types of taxanes. We studied 24 patients receiving chemotherapy, including seven receiving paclitaxel and carboplatin chemotherapy, through a peripheral intravenous catheter in a chemotherapy unit for outpatients of a university hospital in Japan. Ultrasonography images of venipuncture sites were obtained before catheter insertion and immediately before catheter removal. We observed subcutaneous edema in the absence of visible manifestations at the puncture sites of all patients undergoing paclitaxel and carboplatin chemotherapy, but not in any patients receiving other types of taxanes. When vesicant agents and vehicles have caused subclinical subcutaneous edema, clinical nurses may detect early slight extravasation by using ultrasonography.**

Keywords: Chemotherapy, peripheral intravenous catheter, subcutaneous edema, ultrasonography

1. Introduction

Paclitaxel, a taxane, is frequently administered intravenously as an anticancer agent because there is published evidence that weekly administration of paclitaxel after a standard adjuvant chemotherapy regimen improves disease-free and overall survival in women with breast cancer (*1*). Needless to say, clinical nurses must take precise care to avoid extravasation during administration of vesicant drugs, including paclitaxel.

Extravasation is the process by which any liquid accidentally leaks out of a blood vessel into the surrounding tissue. Specifically, in the context of cancer therapy, extravasation refers to the inadvertent infiltration of chemotherapy agents into the subcutaneous or subdermal tissues surrounding an intravenous or intra-arterial administration site (*2*). Such inadvertent infiltration of vesicant anticancer agents (*e.g.*, taxanes) can cause adverse events such as tissue necrosis or induration in the region of catheter placement (*3-5*). The reported incidence of extravasation varies greatly because there is no shared register of chemotherapy extravasation events; however, several studies have been published, most of which have reported that the incidence of extravasation is greater with paclitaxel than

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with other taxanes (*6,7*).

Therefore, maximal detection and assessment of abnormalities suggestive of extravasation is required to better manage administration of taxanes, especially paclitaxel. When a peripheral intravenous catheter is used for paclitaxel infusion, clinical nurses often observe phenomena such as slight swelling, lack of blood return and resistance to infusion at the catheter placement site. The causes of such phenomena at the puncture site have not yet been clearly elucidated except for identification of extravasation and flare reactions; whereas systemic adverse effects of taxane chemotherapy such as arthralgia and myalgia have been better documented (*8-11*). There remains a lack of data concerning subcutaneous tissue or vessel damage in patients undergoing taxane infusion at the catheter placement site because these adverse effects cannot be directly observed. We may know the cause of phenomena such as lack of blood return or resistance to infusion, if we can observe directly the subcutaneous tissue, blood vessel and placed catheter.

We therefore implemented ultrasonography, which has the advantages of being non-invasive, providing real-time information, and being easy to use in the clinic, to enable visualization of subcutaneous tissues and veins (*12,13*). We visualized the puncture sites for infusion therapy with ultrasonography and examined the tissues surrounding the catheterized veins (*14,15*), to determine whether ultrasonography would enable early detection of subcutaneous abnormalities, even in patients who had completed treatment and had no symptoms or visible evidence of such abnormalities.

It has recently been shown in Japan that conventional-TC (paclitaxel with carboplatin every 3 weeks) and dose dense TC (dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks) are effective regimens for paclitaxel administration (*16*). The target hospital also adopted these regimens. Therefore, we obtained typical ultrasonography images of subcutaneous tissues and veins of patients undergoing paclitaxel and carboplatin chemotherapy and compared images obtained immediately before catheter removal with those of patients receiving other types of taxane-based chemotherapy.

2. Materials and Methods

2.1. *Study design and setting*

We did cross sectional observational study of patients (over 20 years old) undergoing taxane-based chemotherapy through a peripheral intravenous catheter in a chemotherapy unit for outpatients in a university hospital in Japan, from February to October 2015.

2.2. *Ultrasound scanning technique*

We visualized venipuncture sites by ultrasonography before catheter insertion and immediately before catheter removal. We evaluated the subcutaneous tissues around the relevant vein using portable ultrasonography equipment (Noblus; Hitachi, Tokyo, Japan) with a linear-array transducer (5-18.0 MHz) under the following conditions: echo gain, 25 dB; dynamic range, 65 dB; and focus range and image depth, 1.5-2.5 cm to show the catheterized vein clearly. In this study, one well-trained researcher performed all ultrasonographic examinations and identified all visible subcutaneous-edema related manifestations and another ultrasonographer with more than 20 years of experience evaluated the ultrasonography images. We defined subcutaneous edema as a cobblestone-like pattern in the subcutaneous fat layer on ultrasound images (*14,15*).

2.3. *Study procedure*

Characteristics of participants (age, sex, body mass index, and site of cancer) were collected from medical records. In macroscopic observation, a clinical nurse and researcher made the judgment of signs (swelling and redness). The information was classified into three types of taxane-based chemotherapy (paclitaxel and carboplatin, docetaxel, and nab-paclitaxel chemotherapy) and showed. Also, we described one conventional-TC case as representative case.

2.4. *Ethical considerations*

This study was approved by the Research Ethics Committee of the Graduate School of Medicine, The University of Tokyo (No. 10712). All participants were informed about the purpose of the research and methods of this study and advised that they were free to withdraw their consent at any time. The researchers obtained written consent from all participants before enrollment in the study.

3. Results and Discussion

3.1. *Characteristics of participants*

Table 1 shows the characteristics of the patients undergoing chemotherapy. The study cohort comprised 24 patients, including seven patients undergoing paclitaxel and carboplatin chemotherapy, eight undergoing docetaxel chemotherapy, and nine undergoing nab-paclitaxel chemotherapy. Patients undergoing paclitaxel and carboplatin chemotherapy received more doses of taxanes over a longer infusion time (average dose of taxanes 206.4 ± 79.4 mg and duration 2.5 hours or 1.0 hour) than those receiving the other two types of taxane-based chemotherapy (105.5 ± 18.5 mg, 1.0 hour, and 185.6 ± 67.2 mg, 0.5 hour, respectively) (Table 1). One patient (paclitaxel and carboplatin chemotherapy group) was needed catheter

placement again, because extravasation occurred due to pulling out catheter accidentally with moving to the toilet. All other patients were able to complete administration of anticancer agents.

Figure 1 shows typical transverse ultrasound images of puncture sites. We observed severe subcutaneous edema after administration of paclitaxel and carboplatin (A2) in patients who had no detectable edema before the infusion (A1). The catheter tip was characteristically visible but the vein not clearly identifiable because of compression by the edema and the absence of an intraluminal anechoic area around the catheter (A2). In comparison, we observed no such changes in the subcutaneous tissues in patients receiving the other two types of chemotherapy (B1, B2, C1, C2). The vessel lumens were clearly visible (anechoic area) in images obtained both before and after administration of docetaxel or nab-paclitaxel (B2, C2).

Table 2 shows our findings concerning subcutaneous edema and related visible manifestations. We observed neither subcutaneous edema nor related visible manifestations around the puncture sites of patients receiving docetaxel or nab-paclitaxel, whereas all patients receiving paclitaxel and carboplatin showed

Table 1. Demographic characteristics and anticancer agents

Items	Paclitaxel and Carboplatin (*n* = 7)	Docetaxel (*n* = 8)	Nab-paclitaxel (*n* = 9)
Age (years)	59.3 ± 12.4	60.9 ± 12.7	62.1 ± 8.6
Sex / female	7 (100.0)	5 (62.5)	5 (55.6)
Body mass index (kg/m^2)	19.2 ± 3.3	22.3 ± 2.6	21.9 ± 2.9
Cancer	Ovary, 4 (57.1)	Breast, 5 (62.5)	Pancreas,7 (77.8)
	Uterine, 3 (42.9)	Prostate, 3 (37.5)	Breast, 2 (22.2)
Anticancer agents	PTX + CBDCA, 6 (85.7)	DOC, 5 (62.5)	Nab-PTX + GEM, 7 (77.8)
	PTX + CBDCA + BEV, 1 (14.3)	DOC + CPA, 2 (25.0)	Nab-PTX, 2 (22.2)
		DOC + PER + TRA, 1 (12.5)	
Dose of taxanes (mg)	206.4 ± 79.4	105.5 ± 18.5	185.6 ± 67.2
Drip rate of taxens (mL/h)	225.7 ± 44.3	280.0 ± 0.0	75.6 ± 26.1
Drip time of taxens	2.5 hours, 5 (71.4)	1.0 hour, 8 (100.0)	0.5 hour, 9 (100.0)
	1.0 hour, 2 (28.6)		

Mean ± SD or *n* (%). PTX; paclitaxel, CBDCA; carboplatin, BEV; Bevacizumab, DOC; docetaxel, CPA; cyclophosphamide, PER; pertuzumab, TRA; Trastuzumab, Nab-PTX; nab-paclitaxel, GEM; gemcitabine.

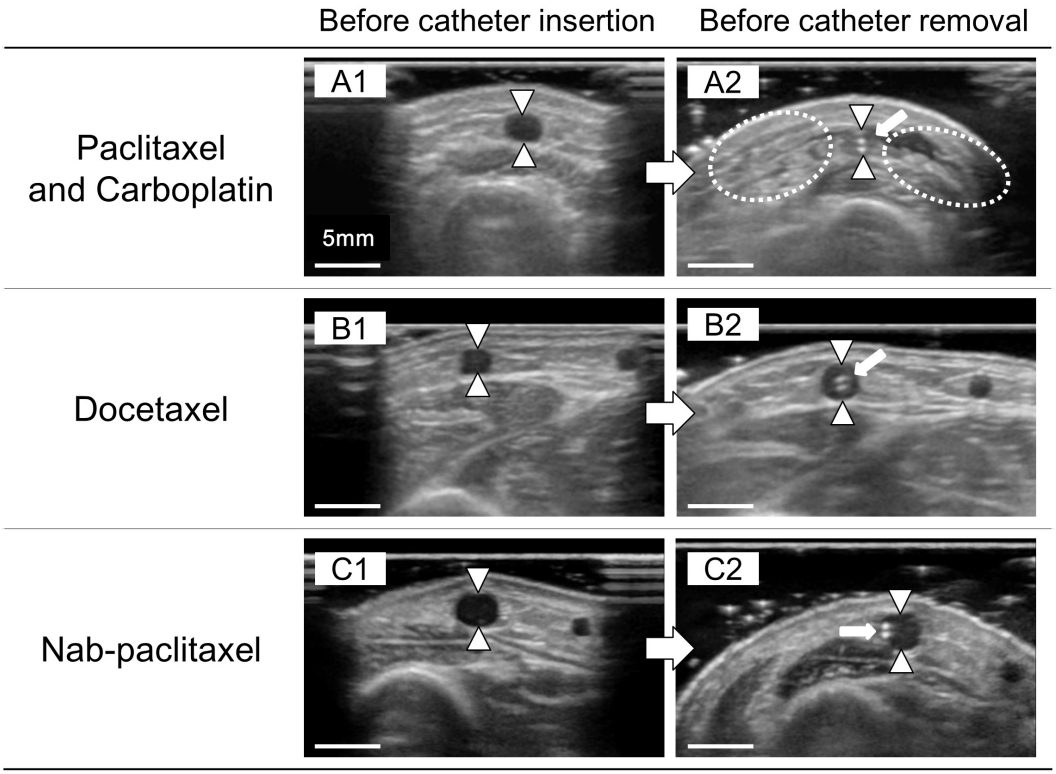

Figure 1. Ultrasound images of veins and subcutaneous tissues at puncture sites of patients undergoing three types of taxane-based chemotherapy. Transverse ultrasound images of puncture sites obtained before catheter insertion **(A1, B1, C1)** and after administration (before catheter removal: **A2, B2, C2)**. Arrowheads indicate the catheterized vein and allow indicate the catheter tip; the catheter tip can be seen as two bright points in the vein. Subcutaneous edema is visible around the catheterized vein in the area circled by a dotted line in a patient undergoing paclitaxel and carboplatin administration **(A2)**.

ultrasonographic evidence of subcutaneous edema at their puncture sites after administration of these chemotherapy agents. Furthermore, we encountered clinical problems such as lack of blood return, difficulty in continuing the infusions, and swelling during administration of paclitaxel and carboplatin. Only one patient who received this regimen did not show macroscopic symptoms. Extravasation occurred in one patient, necessitating reinsertion of the catheter to complete the chemotherapy.

3.2. *Representative case: conventional-TC (paclitaxel with carboplatin every 3 weeks)*

A 79-year-old woman with ovary cancer developed severe subcutaneous edema around her puncture site after paclitaxel and carboplatin administration (Figure 2). The nurse had inserted a 24G peripheral intravenous catheter into a forearm vein. There were no visible abnormalities at the puncture site during pre-medication and paclitaxel infusion (paclitaxel 80 mg + natural saline 250 mL, 280 mL/h for one hour). However, no return of blood occurred when a nurse tried to exchange the infusion bags from paclitaxel to carboplatin. The nurse determined that the catheter appeared to be correctly positioned in the vein; however, the catheter tip may have been touching the vein wall. The nurse shifted the catheter tip a little after peeling off the dressing. After adjustment, return of blood was achieved, enabling complete administration of the carboplatin infusion without reinsertion. An ultrasound image after administration showed severe subcutaneous edema (D1, D2), compressing the catheterized vein and thus likely causing a lack of blood return in the absence of any visible manifestations or pain (D3). Ultrasonography confirmed that the tip of the catheter had not dislodged from the vein.

These findings indicate that ultrasonography can identify subcutaneous edema after administration of taxane in patients without visible manifestations or symptoms other than a lack of blood return. Also, paclitaxel may cause subcutaneous edema at the infusion site. Such

Table 2. The subcutaneous edema observed by ultrasonography and macroscopic symptoms

Items	Paclitaxel and Carboplatin (n = 7)	Docetaxel (n = 8)	Nab-paclitaxel (n = 9)
Subcutaneous edema (ultrasonographic observation)	7 (100.0%)	0 (0.0%)	0 (0.0%)
Macroscopic symptoms	Lack of blood return + difficulty of drip + swelling, 2 (28.6%) Lack of blood return + difficulty of drip, 1 (14.3%) Slight swelling, 3 (42.9%) No symptoms, 1 (14.3%)	No symptoms, 8 (100.0%)	No symptoms, 9 (100.0%)

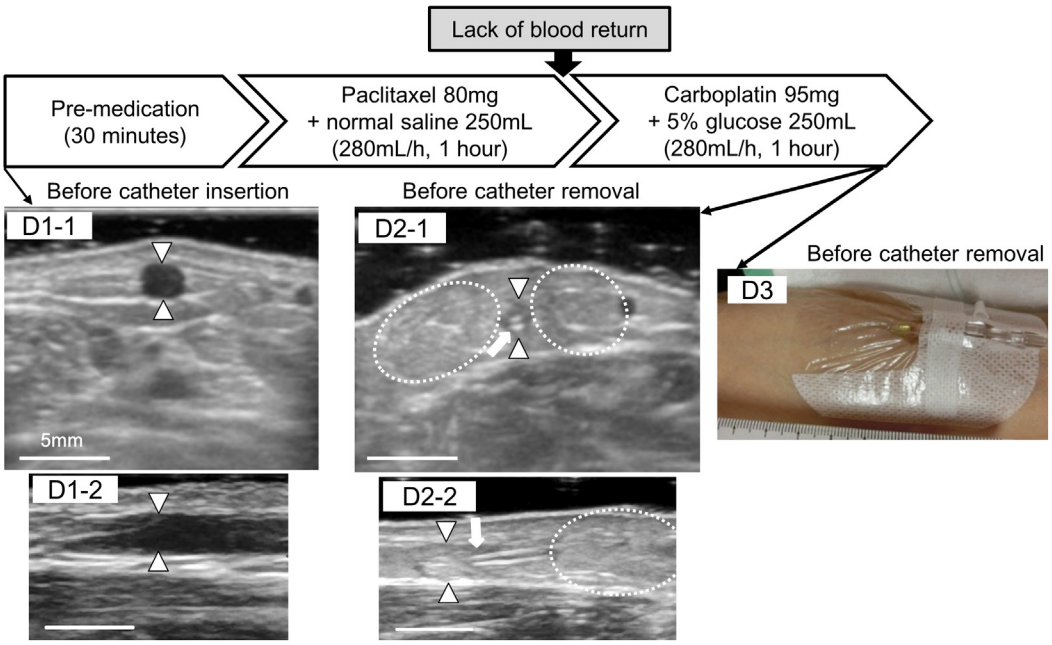

Figure 2. Ultrasound images and a photograph of the puncture site of a 79-year-old female patient. Transverse images **(D1-1, D2-1)** and longitudinal images **(D1-2, D2-2)** at puncture sites obtained before catheter insertion and after administration (before catheter removal). Arrowheads indicate the catheterized vein and allow indicate the catheter tip; the catheter tip can be seen as two bright points and lines in the vein. Subcutaneous edema is visible around the catheterized vein in the areas circled by dotted lines **(D2-1, D2-2)**. Clinical image of the insertion site taken with a digital camera **(D3)**.

edema may compress the vein, leading to a lack of blood return and difficulty in continuing the infusion.

All seven study patients who underwent paclitaxel and carboplatin chemotherapy showed subcutaneous edema after their infusions, whereas we identified no such changes in the ultrasound images of patients receiving docetaxel or nab-paclitaxel chemotherapy. Paclitaxel, docetaxel and nab-paclitaxel are classified as the same taxane; however, the preparations incorporate different vehicles. The vehicle comprises polyethoxylated castor oil and anhydrous ethanol in paclitaxel infusions (*10*). This vehicle reportedly often causes hypersensitivity and vascular irritability (*17,18*). In comparison, polyethoxylated castor oil is not the vehicle for docetaxel and nab-paclitaxel. Some studies have reported that classifying taxanes (including paclitaxel) as vesicants is debatable and that there is insufficient evidence to formally classify antineoplastic agents according to their vesicant properties (*6*). In the current study, patients receiving paclitaxel and carboplatin received more doses of taxanes over a longer infusion time than did patients receiving docetaxel or nab-paclitaxel. The subcutaneous edema may have developed because of stimulation of the vessel wall by antineoplastic agents and/or their vehicle (polyethoxylated castor oil) during lengthy infusions; however, it is unclear whether the subcutaneous edema was attributable to the amount of taxanes or total administration time. Furthermore, it is noteworthy the vein may be compressed by subcutaneous edema when the nurses cannot achieve blood return.

Also, there is a published report of a patient who presented with severe and progressive pain at the infusion site on day 11 after paclitaxel administration, despite having had no evidence of complications during the infusion (*19*). We, therefore, speculated that some changes can occur in the subcutaneous tissue and vein even when there are not significant visible abnormalities or symptoms by the end of chemotherapy. It is possible that ultrasound would provide more detailed information than the infiltration scale (*15*), including enabling detection of early slight extravasation.

Our findings indicate that stimulation by vesicant agents such as paclitaxel may cause subcutaneous edema at the infusion site. Such edema may compress the vein, leading to a lack of blood return and difficulty in continuing the infusion. Prevention of subcutaneous edema stimulated by vesicant agents and their vehicles may require consideration of varying the mode of venipuncture, for example, by choosing a larger vein and selecting a different catheter gauge. Furthermore, both the nurse and patient should be alert to the possibility of subcutaneous edema and inspect the infusion site repeatedly, since such edema may be present by the completion of infusion in the absence of visible manifestations or symptoms.

Because this study was observational study and the number of subjects was small, we could not investigate the cause of the subcutaneous edema. However, the ultrasound findings reported here may be a key to further exploring the adverse events of paclitaxel.

In conclusion, we have here presented typical ultrasound images of the subcutaneous tissues around the catheterized vein after taxane administration and documented ultrasound evidence of severe subcutaneous edema immediately before catheter removal in the absence of significant visible manifestations or symptoms in patients undergoing paclitaxel and carboplatin chemotherapy but not in those receiving other taxane-based chemotherapy regimens.

Both subcutaneous edema stimulated by vesicant agents and their vehicles and early slight extravasation may be identified by clinical nurses by using ultrasonography.

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Conflicts of interest

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References

1. Sparano JA, Wang M, Martino S, Jones V, Perez EA, Saphner T, Wolff AC, Sledge GW Jr., Wood WC, Davidson NE. Weekly paclitaxel in the adjuvant treatment of breast cancer. N Engl J Med. 2008; 358:1663-1671.
2. Pérez Fidalgo JA, García Fabregat L, Cervantes A, Margulies A, Vidall C, Roila F; ESMO Guidelines Working Group. Management of chemotherapy extravasation: ESMO-EONS Clinical Practice Guidelines. Ann Oncol. 2012; 23 (Suppl 7):vii167-173.
3. Hahn JC, Shafritz AB. Chemotherapy extravasation injuries. J Hand Surg Am. 2012; 37:360-362.
4. Schulmeister L. Extravasation management: clinical update. Semin Oncol Nurs. 2011; 27:82-90.
5. Raley J, Geisler JP, Buekers TE, Sorosky JI. Docetaxel extravasation causing significant delayed tissue injury. Gynecol Oncol. 2000; 78:259-260.
6. Barbee MS, Owonikoko TK, Harvey RD. Taxanes: vesicants, irritants, or just irritating? Ther Adv Med Oncol. 2014; 6:16-20.
7. Pérez Fidalgo JA, García Fabregat L, Cervantes A, Margulies A, Vidall C, Roila F. ESMO Guidelines

Working Group. Management of chemotherapy extravasation: ESMO-EONS Clinical Practice Guidelines. Ann Oncol. 2012; 23 (Suppl 7):vii167-173.
8. Chiu N, Chiu L, Chow R, Lam H, Verma S, Pasetka M, Chow E, DeAngelis C. Taxane-induced arthralgia and myalgia: A literature review. J Oncol Pharm Pract. 2017; 23:56-67.
9. Stanford BL, Hardwicke F. A review of clinical experience with paclitaxel extravasations. Support Care Cancer. 2003; 11:270-277.
10. Bicher A, Levenback C, Burke TW, Morris M, Warner D, DeJesus Y, Gershenson DM. Infusion site soft-tissue injury after paclitaxel administration. Cancer. 1995; 76:116-120.
11. Boyle DM, Engelking C. Vesicant extravasation: Myth and realities. Oncol Nurs Forum. 1995; 22:57-67.
12. Yabunaka K, Iizaka S, Nakagami G, Aoi N, Kadono T, Koyanagi H, Uno M, Ohue M, Sanada S, Sanada H. Can ultrasonographic evaluation of subcutaneous fat predict pressure ulceration? J Wound Care. 2009; 18:192-196.
13. Yabunaka K, Konishi H, Nakagami G, Sanada H, Iizaka S, Sanada S, Ohue M. Ultrasonographic evaluation of geniohyoid muscle movement during swallowing: a study on healthy adults of various ages. Radiol Phys Technol. 2012; 5:34-39.
14. Yabunaka K, Murayama R, Takahashi T, Tanabe H, Kawamoto A, Oe M, Arai R, Sanada H. Ultrasonographic appearance of infusion via the peripheral intravenous catheters. J Nurs Sci Eng. 2015; 2:40-46.
15. Yabunaka K, Murayama TR, Tanabe H, Takahashi T, Oe M, Oya M, Fujioka M, Sanada H. Ultrasonographic classification of subcutaneous edema caused by infusion via peripheral intravenous catheters. J Med Ultrasound. 2016; 24:60-65.
16. Katsumata N, Yasuda M, Takahashi F, Isonishi S, Jobo T, Aoki D, Tsuda H, Sugiyama T, Kodama S, Kimura E, Ochiai K, Noda K; Japanese Gynecologic Oncology Group. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: A phase 3 open-label, randomized trial. Lancet. 2009; 374:1331-1338.
17. Kawano S, Kondoh H, Ishikawa K, Koizumi S, Kadota T, Takahashi N. Irritability study of paclitaxel in rabbit ear vein. J Toxicol Sci. 1994; 19:123-130.
18. Singla AK, Garg A, Aggarwal D. Paclitaxel and its formulations. Int J Pharm. 2002; 235:179-192.
19. Herrington JD, Figueroa JA. Severe necrosis due to paclitaxel extravasation. Pharmacotherapy. 1997; 17:163-165.

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